UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/508,254	10/02/00	CHARETTE M	CIBT-P01-558

028120
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HM12/1023

EXAMINER
DEBERRY, R

ART UNIT	PAPER NUMBER
1647	8

DATE MAILED: 10/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application N .	Applicant(s)	
	09/508,254	CHARETTE ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-29* is/are pending in the application.

4a) Of the above claim(s) *2-10,12 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,13,15-24,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-13 and 15-29* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647, Regina M. DeBerry.

Status of Application, Amendments and/or Claims

The amendment filed 19 September 2001 (Paper No. 7) has been entered in full. Claim 14 was cancelled. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the grounds that the subject matter is closely related and there is no indication that a search for one group will not retrieve relevant prior art for the other groups. Applicant has amended the claims to include the features of claim 24 (Group V) with the expectation that Groups I and V will be rejoined. Applicant has elected the following species: peripheral nervous system cells, OP-1, and GDNF. Applicant states that claims 1, 24, 28 and 29 are generic and all claims, except 12 are readable on the elected species. Applicant's argument has been fully considered and deemed partly persuasive. Group V (claim 24) will be rejoined with Group I (claims 1, 11,13, 15-23, 28,29). The Groups I-IV, VI-VII are drawn to methods which comprise different steps, diverse population of subjects and different cellular functions. A search and examination of all these methods in one patent application would result in an undue burden, since the searches for the methods are not co-extensive, the classification is different, and/or the subject matter is divergent.

The requirement is still deemed proper and is therefore made FINAL. Claims 2-10,12, 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group (12 is drawn to a nonelected species), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Priority

A claim to priority under 371 must contain a specific reference to such in the first paragraph of the first page of the specification.

This application discloses and claims only subject matter disclosed in prior Application No. 371 of PCT/US98/18772, filed 09 September 1998, and names an inventor or inventors named in the prior application. Accordingly, this application may constitute a continuation or division. Should applicant desire to obtain the benefit of the filing date of the provisional application, attention is directed to 35 U.S.C. 119(e).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The specification is objected to because the Brief Description of the Drawings refers solely to Fig 1. however the drawing has Fig 1A and Fig 1B. Appropriate correction is required.

Claim Objections

Claims 11, 13,18, 19 and 23 are objected to because of the following informalities:

Claims 18 and 23 encompass non-elected inventions and require amendment to limit to elected invention. Appropriate correction is required.

Claim 11, 13, 19 and 23, depend on claims drawn to a non-elected group. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,11,13,15-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for promoting survival or outgrowth of neurites comprising contacting peripheral nervous system cells with OP-1 and NT-3 or OP-1 and GDNF *in vitro*, does not reasonably provide enablement for the methods as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1,11,13,15-24 are generally drawn to a method for promoting survival or growth of mammalian neural cells, wherein said cells express an OP/BMP-activated serine/threonine kinase receptor and a GDNF/NGF-activated tyrosine kinase receptor, comprising: contacting neural cells with a preparation comprising a GDNF/NGF neurotrophic factor and an OP/BMP morphogen having an amino acid sequence with at

least 70% homology with the C-terminal seven cysteine skeleton of human OP-1 (claim 1) or wherein said OP/BMP morphogen comprises an amino acid sequence having at least 80% homology with the C-terminal seven-cysteine domain of human OP-1 (claim 15), or wherein said OP/BMP morphogen comprises an amino acid sequence having at least 60% amino acid identity with the C-terminal seven-cysteine domain of human OP-1 (claim 16) or wherein said OP/BMP morphogen comprises an amino acid sequence having at least 70% amino acid identity with the C-terminal seven-cysteine domain of human OP-1 (claim 17).

In order to make a sequence variant, for example, with the reasonable assurance that it would have the desirable properties of the invention, the artisan would need to know which regions of the disclosed polypeptide are responsible for the interactions underlying its biological function(s). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed. The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working

example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed.

For sequences having one or two substitutions, for example, the artisan would reasonably expect that many of the possible variants would retain functional properties comparable to those of the unmodified protein, and it would require only routine manipulations to make and test a reasonably representative sampling of the possible variants. However, as the number of modified sites increases, the number of possible variants, and hence the degree of experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo *et al.*, 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Furthermore, claim 24 is drawn to a method for promoting the survival or growth of mammalian cells, wherein said cells express an OP/BMP-activated serine/threonine kinase receptor and a GDNF/NGF-activated tyrosine kinase receptor, comprising contacting said cells with an effective concentration of a preparation comprising: a GDNF/NGF neurotrophic factor, and an OP/BMP morphogen. The specification discloses examples using the claimed method in peripheral neural cells. The specification is not enabled for promoting the survival or growth of all/every type of mammalian cell.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity in every type of mammalian cell, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 28 is drawn to a pharmaceutical preparation for promoting the survival or growth of mammalian neural cells comprising a GDNF/NGF neurotrophic factor and an OP/BMP morphogen. Claim 29 is drawn to a pharmaceutical preparation for inhibiting the death or degeneration of mammalian neural cells comprising a GDNF/NGF neurotrophic factor and an OP/BMP morphogen. Claims 28 and 29 are not enabled for pharmaceutical preparations. The specification fails to disclose a direct correlation (working examples, animal models, etc.) between the use of the instant invention and treatment in subjects for conditions such as Alzheimer's disease, severed nerve fibers, and strokes (specification pages 23-25). Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light. Buckel points out the difficulties using proteins for treatment such as optimization and administering of proteins, solubility and possible side effects (see Buckel, Trends in Pharmacology

Science, 1996 Vol. 450-456). Furthermore, claim 29 is not enabled for the property of inhibiting death or degeneration. Example 1 demonstrates an *in vitro* effect of enhanced process formation in neural cells which is different from inhibition of death and degeneration of neural cells.

Due to the large quantity of experimentation necessary to develop the parameters for the optimization and delivery of the instant pharmaceutical composition and to evaluate survival or growth of neural cells in a mammalian subject upon administration of the instant pharmaceutical composition, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention and the contradictory state of the prior art (see discussion above and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1,11,13,14-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Bengtsson *et al.* The claims are generally drawn to a method for promoting survival

or growth of neural cells, wherein said cells express an OP/BMP-activated serine/threonine kinase receptor and a GDNF/NGF-activated tyrosine kinase receptor, comprising contacting neural cells with a preparation comprising an OP/BMP morphogen having an amino acid sequence with at least 70% homology with the C-terminal seven cysteine skeleton of human OP-1 and a GDNF/NGF neurotrophic factor. Bengtsson *et al.* teaches the mapping of the receptors for ligand OP/BMP. The receptor for this ligand is BMPR-II which is a serine kinase receptor. The receptors for ligands GDNF and NGF, named Ret and Trk respectively, are tyrosine kinase receptors. They were all mapped in different neurons in the peripheral ganglia and spinal cord of the chicken embryo. Bengtsson teaches the use and concentrations of factors OP-1 and GDNF. Bengtsson *et al.* discloses that OP-1 and GDNF act synergistically to promote survival or growth in chicken neurons such as the peripheral ganglia (please see reference, especially abstract, pgs 561, 3rd paragraph-562 and pgs 563, 2nd paragraph-566).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 11,13, 15-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lein *et al.* in view of Durbec *et al.* Lein *et al.* discloses that exposure of sympathetic neurons with OP-1 and NGF as a cofactor influences dendritic growth in sympathetic neurons. Lein *et al.* also discloses concentrations of the factors (please see reference especially abstract, the experimental procedures, figure 3, page 204, 4th paragraph, pg 212, 3rd paragraph and pg 213, 4th paragraph). Lein *et al.* does not teach the combination of OP-1 and GDNF for promoting survival or growth of neural cells. Durbec *et al.* discloses a functional interaction between the Ret receptor and the factor GDNF and that GDNF is essential for the development of the peripheral nervous system. Durbec *et al.* also discloses that neurons of the peripheral nervous system express high levels of c-ret (please see reference especially abstract, pg 790, 1st paragraph and pg 791, 1st paragraph). It would obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Lein *et al.* and Durbec *et al.* to substitute NGF with GDNF. The person of ordinary skill in the art would have been motivated to make the modification because GDNF belongs to transforming growth factor β superfamily which is the same superfamily as OP-1 and would expect

success because all three factors (GDNF, OP-1, NGF) have been shown to have a positive effect on growth, survival and/or differentiation of neural cells.

Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lein *et al.* and Durbec *et al.* as applied to claims 1,13,15-24 above, and further in view of Weiss *et al.* US Patent No 5,851,832 and Weiss *et al.*, US Patent No 6,294,346. For the purpose of this rejection, the term "pharmaceutical" as recited in the claims is interpreted as an intended use of the composition in therapy. This intended use is accorded little patentable weight. The teachings of Lein and Durbec are discussed above. Lein and Durbec do not disclose a pharmaceutical preparation comprising GDNF/NGF neurotrophic factor and OP/BMP morphogen. Weiss *et al.* discloses the pharmaceutical preparation comprising GDNF/NGF neurotrophic factor and OP/BMP (please see US Patent No. 5,851,832 especially column 1, lines 38-55; column 4, lines 12-25; column 10, lines 43-47; column 11, lines 31-34; column 12, lines 23-31; column 26, lines 42-column 27, lines 8; column 29, lines 61-column 30, lines 19; column 31, lines 1-34. Also see Weiss *et al.* US Patent No 6,294,346 especially abstract, column 1, lines 39-56; column 4, lines 16-30; column 11, lines 36-38; column 12, lines 32-36; column 26, lines 65-column 27, lines 32; column 30, lines 20-47; column 31, lines 29-63 and claims. Therefore it would be obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Lein and Durbec and combine the teachings of Weiss because all of the teachings implicate these factors in growth and/or differentiation of neural cells. The person of ordinary skill in the art would be motivated to make a pharmaceutical preparation because the composition could help in

the treatment of various neurological diseases and would have expected success based on the working examples of Weiss *et al.* The compositions of Weiss *et al.* are not inconsistent with the use in therapy since they do not adversely affect live cell in culture.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD

RMD
October 12, 2001

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER